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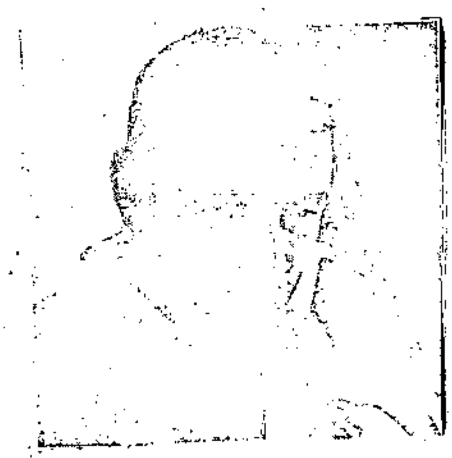

Feliks Zalmanovich Meyerson, Doctor of Medical Sciences and Chief of the /74* Laboratory of Experimental Cardiology of the Institute of Normal and Pathological Physiology of the Academy of Medical Sciences, USSR. He is a physiologist and a student of V.V. Parin. He is presently occupied with a study of the mechanism of human adaptation to basic evnironmental factors and with the prevention of circulatory diseases. He is the author of scientific studies in the fields of physiology and cardiology, as well as in the molecular mechanisms of adaptation of the organism. These works include a monograph: Hyperfunction, Hypertrophy and Cardiac Deficiency [Giperfunktsiya, Gipertrofiya, Nedostatochnost' Serdtsa] Moscow, 1968, New York, 1969, as well as a popular scientific book: Physiology and Molecular Biology [Fiziologiya i Molekulyarnaya Biologiya], Moscow, "Nauka Press", 1970. He discovered (together with V.V. Parin et al.) the phenomenon of autodesympathization - exhaustion of the reserves of catecholamines in the myocardium during cardiac stress.

*Numbers in the margin indicate pagination in the foreign text.

As is known, in people and in animals who arrive at a high altitude without preliminary preparation - under conditions of oxygen deficiency (hypoxia) - one observes noticeable disruptions in behavior and work activity. These disruptions cannot be eliminated by increasing pulmonary ventilation, by increasing the minute volume of the heart, the mass of circulating blood, or by other methods of struggling for oxygen. However, with the passage of time the activity of the organism under conditions of altitude hypoxia is gradually restored, while the degree of hyperventilation and of other signs of the "struggle for oxygen" decreases. A stable adaptation to oxygen deficiency develops - and economical and reliable adaptation to altitude hypoxia. The mechanism of this adaptation - a means by whose aid an organism not adapted to oxygen deficiency changes into an organism capable of living under the conditions of altitude - is an important problem of biology and medicine.

Studies which have been set up on this problem in many countries of the world were made necessary by the need for solving certain urgent problems thrust to the fore by life itself. Chief among them are: adaptation to hypoxia by large human contingents newly arrived in mountainous areas; adaptation of workers to the simultaneous actions of altitude hypoxia and physical stress; the capacity to carry out complex forms of intellectual activity vital for controlling modern apparatus at high altitudes; altitude illness in mountains and deadaptation following decent from the mountains; finally, a new and extremely important problem - the use of adaptation to hypoxia with the goal of increasing the organism's resistance to the most varied conditions.

Each of the enumerated problems is important to an extent sufficient to make it the subject of an independent investigation, while together with this, no single one of them can be solved without an understanding of the very essence of the process of adaptation. The absence of a clear concept of the principal mechanism of adaptation to a significant degree delays a solution of practical problems.

In recent years a certain process has been noted, thanks chiefly to the development of general concepts concerning adaptation of the organism to the environment and to the use of the achievements of molecular biology.

The Transport and Cellular Factors of Adaptation

Altitude hypoxia is not a stimulus addressed to any particular organ of the senses; it does not act primarily on the exteroreceptors[1]; but rather unnoticed, it gradually invades the internal medium of the organism, causing oxygen deficiency in the blood - hypoxemia. Hypoxemia acts as a stimulus on the chemo-receptors of /75 the aortal-carotid zone, directly on the centers which regulate respiration and circulation, and on other organs, thus increasing the adaptive function of the systems responsible for oxygen transport and distribution in the organism: primarily the system of respiration and circulation.

It is extremely significant that notwithstanding the mobilization of the oxygen transport system, hypoxemia in the event of significant altitude hypoxia is not eliminated, and a decrease occurs in the oxygen tension in the cells of the brain, muscles and other organs. This limits the intensity of oxydation and oxydation phosphorylation and becomes the cause of insufficient production of adenosintriphosphoric acid (ATP) by each mitochondrium.

ATP is the main source of energy for all forms of vital activity. A deffficiency of ATP during acute hypoxia leads to disruption of the organism's functions or, in a better case, limits its behavioral activity.

The adaptation subsequently developing does not simply ensure the survival of the organism under new environmental conditions, but makes possible the restoration of its normal activity in spite of the defficiency of oxygen in the environment. This means that adaptation in some way restores the formation of the needed amount of ATP in the cells of the organism. To discover the mechanism of adaptation means to comprehend how, and at what cost the organism solves this problem.

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1 Exteroreceptors - specialized neural or epithelial formations which perceive stimuli acting on the organism from the environment; chemoreceptors - nerve endings which are excited under the influence of changes in the chemical composition of the ambient medium.

Studies made over the last decade have made it possible to conclude that adaptation to hypoxia occurs as the result of two basic factors. First, as the result of an increase in the capacity and effectiveness of functioning of the oxygen transport systems, i.e., the systems of external respiration, circulation, and blood. Second, as the result of an increase in the capacity of the oxygen utilization system and of ATP resynthesis in the cells. The given change makes possible adequate extraction of oxygen from the blood and resynthesis of ATP in the cells, hypoxemia notwithstanding.

The concept that these two factors, finely coordinated between themselves, determine the development of adaptation is an important step forward. However, it leaves open one important question: by what means does the organism provide for a stable increase in the capacity of the systems of utilization and oxygen transport, comprising the very basis of adaptation?

Over the course of recent years, our laboratory has been based on the concept that a decisive role in an increase in the capacity of the systems of utilization and transport of oxygen is played by activation of the synthesis of nucleic acids and proteins, developing principally during adaptation to hypoxia. Experiments have shown that an increase in synthesis is observed with full constancy, during adaptation to hypoxia, in the oxygen transport systems, i.e., in the system of the blood, in the heart, the lungs, and also in systems which do not have a direct relationship to oxygen transport, primarily in the brain.

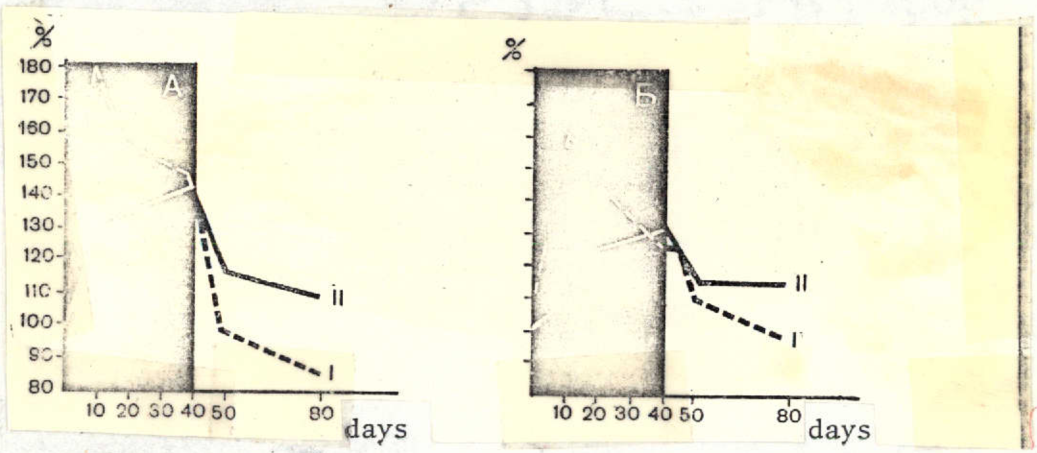


Fig. 1. Dynamics of protein synthesis in the myocardium (I) and the weight of the ventricles of the heart (II) during adaptation to the discontinuous effect of altitude hypoxia. Along the axis of the ordinate - control indices (in %); along the axis of the abscissa - time from the beginning of the experiment. Duration of action of the hypoxia - 40 days (this period of time both here and in the remaining drawings is shaded). Activation of synthesis is the right ventricle during adaptation to hypoxia is more pronounced, and the weight of the ventricle increases more. This is explained by the increasing load on the right ventricle.

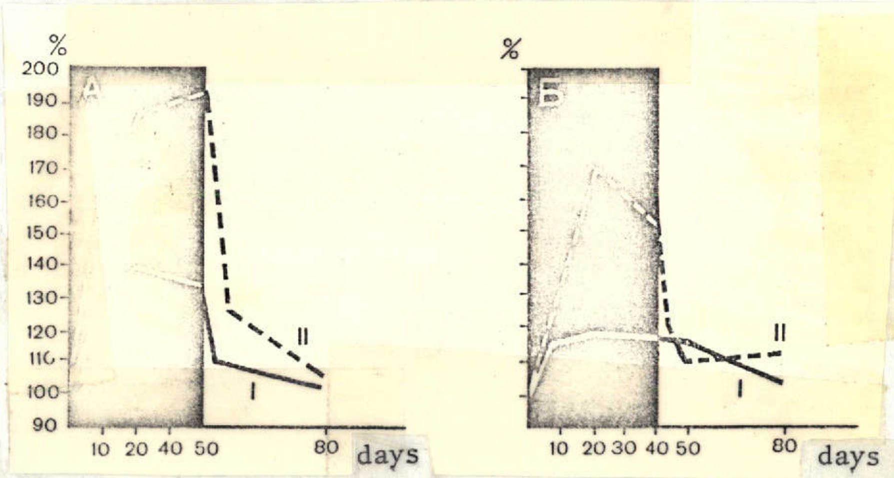


Fig. 2. Dynamics of concentration (I) and total content (II) of RNA in the ventricles of the heart during adaptation to hypoxia (symbols along the axes of the coordinates are the same as in fig. 1). One can see that during adaptation to hypoxia the RNA content of the heart sharply increases. This is vital for an increase in protein biosynthesis.

The Role of Nucleic Acid and Protein Synthesis in the Development of Adaptation /76

For the purpose of studying the role of nucleic acid and protein synthesis in the development of adaptation, animals were daily placed for six hours in a pressure chamber and "elevated" to an "altitude" of 6-7 thousand meters; adaptation developed gradually - after 40-45 such sessions of hypoxia.

Following the beginning of the hypoxis effects, the synthesis of proteins, determinable in the right ventricle of the heart by including the labeled amino acid methionine, shows an increase of 80% (fig. 1, dotted line). During this process, the weight of the ventricle increases by 28% - the heart undergoes hypertrophy. Subsequently, synthesis somewhat decreases, while the weight of the ventricle becomes stable. Cessation of hypoxic effects entails, as is shown in fig. 1, a significant decrease in the intensity of synthesis and inverse development of hypertrophy. As the result of adaptation, the RNA content in the right ventricle of the heart increases by 90%, while in the left - by 60%. Following cessation of adaptation, the RNA content precipitously falls and is restored to the normal level (fig. 2).

Hence, in the heart one observes a pronounced activation of nucleic acid and protein synthesis which occurs through adaptive hyperfunctioning during adaptation to hypoxia.

In differentiation to the heart, the cerebral cortex does not hyperfunction during hypoxia and is a system which is most profoundly and earliest injured by hypoxia. Activation of biosynthesis in the cerebral cortex develops gradually (fig. 3A). 10 days from the beginning of exposure to hypoxia, the RNA concentration increased by a total of 15%. Then the increase gradually progresses and by the 40th day reaches 50%. The intensity of protein synthesis, determined by the inclusion of labeled methionine, increases proprotional to the concentration of RNA, and by the end of the experiment reaches 80%.

Investigations of protein synthesis in the cerebral cortex show that in the process of adaptation to hypoxia, the inclusion of labeled methionine in the giant pyramid cells of the cortex increases, and by the 40th day reaches 180% of the control level (fig 3b). The inclusion of protein in the nuclei of the glial satellite cells surrounding these neurons increased by 300% in comparison with the control (3c). The dynamics of the cellular dimensions of the cortical zone under the examination show that in the process of adaption to hypoxia, the dimensions of the pyramid neurons increase, on the average, by 35%, while the dimensions of the nuclei of the glial cells, on the other hand, decrease by 50-60%. This significant aspect of the process was revealed in our experiments, conducted together with D. Krantz from the German Democratic Republic and T.S. Zadraliyev[1]. A decrease in the size of glial cells, with a simultaneous activation of synthesis in them produces the impression of a paradox. The most probable

1 "DAN USSR" vol. 203, 1972, Nr. 3.

explanation for this phenomenon consists in that materials synthesized in the glial cells do not remain there, but are used by the neurons, whose size increases. The glial cells, as it were, fulfill the function of "donors". In any case, this picture clearly reappears both during adaptation to conditions of discontinuous pressure chamber hypoxia, and during adaptation to high-mountainous conditions, at an elevation of 3200 m.

Leaving the mechanism of this activation of synthesis for later presentation, one principal feature should be emphasized.

The demonstrable activation of synthesis of nucleic acids and proteins does not simply accompany adaptation, but rather plays a role in it as a vital branch of the process. What is the logic behind this statement?

Our experiments showed that the actinomycin which inhibits RNA synthesis, disrupts adaptation, decreases the organism's consumption of oxygen and leads to the death of most of the animals. The administration of this preparation over the course of 5 days, between the 20th and the 25th days of adaptation to hypoxia in a dose which does not cause death in the control animals, led to the death of 65% of the adapting animals. Among the surviving animals, disruption of oxygen consumption was observed. As is known, in unadapted animals, during the first ascent to an altitude of 7000 m, oxygen consumption decreases by about 30%. In the process of adaptation, this defect in oxygen consumption gradually decreases, and by the 25th day of adaptation the animals consume almost as much oxygen as at sea level. This phenomenon, discovered by Le. M. Krebs and N.A. Verzhbinskaya in 1956[1], is a clear reflection of the organism's adaptation to oxygen deficiency is the environment. The administration of actinomycin entirely eliminates this achievement of adaptation. After 5 days of the administration of this inhibitor, the defect in oxygen consumption once again comprises 26%. In adapted animals another important phenomenon also develops under the influence of actinomycin, namely a decrease in oxygen consumption not only under pressure chamber conditions, but also under ordinary conditions. Hence, these experiments indicate that the defect in oxygen consumption at inhibition of RNA synthesis is also observed in the presence of oxygen deficiency in the environment - in the absence of increased

1 Le. M. Krebs et al., "Fiziol. zhurnal SSSR" Vol. 42, 1956, Nr. 2.

load on the functions of external respiration and circulation. In connection with this, it should be recalled that actinomycin - an inhibitor of RNA synthesis - also damages the structure of the organism where RNA synthesis most intensively occurs. On the basis of the given principle, in the experiments of I.R. Tat, actinomycin suppressed, for example, the activation of formation of mitochondria, induced by the hormone thyroxin. One can assume consequently, that during adaptation to altitude hypoxia activation of nucleic acid and protein synthesis occurs primarily in the system of the mitochondria; inhibition of this adaptive activation of the formation of the mitochondria comprises the most probable basis of the effect of actinomycin. Such an assumption essentially represents an attempt to postulate activation of the formation of the mitochondria as an important factor of adaptation to hypoxia.

MITOCHONDRIA AND ADAPTATION /77

In order to verify the concept concerning the role of the formation of mitochondria in adaptation to hypoxia the author, together with V.D. Pomoynitskiy investigated the synthesis of DNA, RNA, and protein in the nuclei and mitochondria of the cardiac and skeletal muscles during adaptation to the effects of pressure chamber, altitude hypoxia[1]. One can surmize (fig. 4), that the intensity of DNA systhesis, determinable by means of the labeled DNA precursor, thymidine, increases by the 10 day of adaptation 9-fold for the right ventricle and 4-fold for the left ventricle. This multiple increase in the biosynthesis of DNA, as shown in figure 4, is maintained without signficant changes over the course of the subsequent 30 days of adaptation. As a result the concentration of DNA in the mitochondria increases 2.5 times over a 10 day period for the right ventricle, and 90% for the left. Over the course of the subsequent period of adaptation, concentration of mitochondrial DNA remains at this level.

During an evaluation of these data, it is important to bear in mind that in the nuclei of the muscle cells of the cardiac ventricles in the norm, during any stress on the heart, and during adaptation to hypoxia, the synthesis of DNA is not observed. At the same time the mitochondria, which we investigated, were in an

1 DAN SSSR, Vol. 203, 1972, Nr. 4

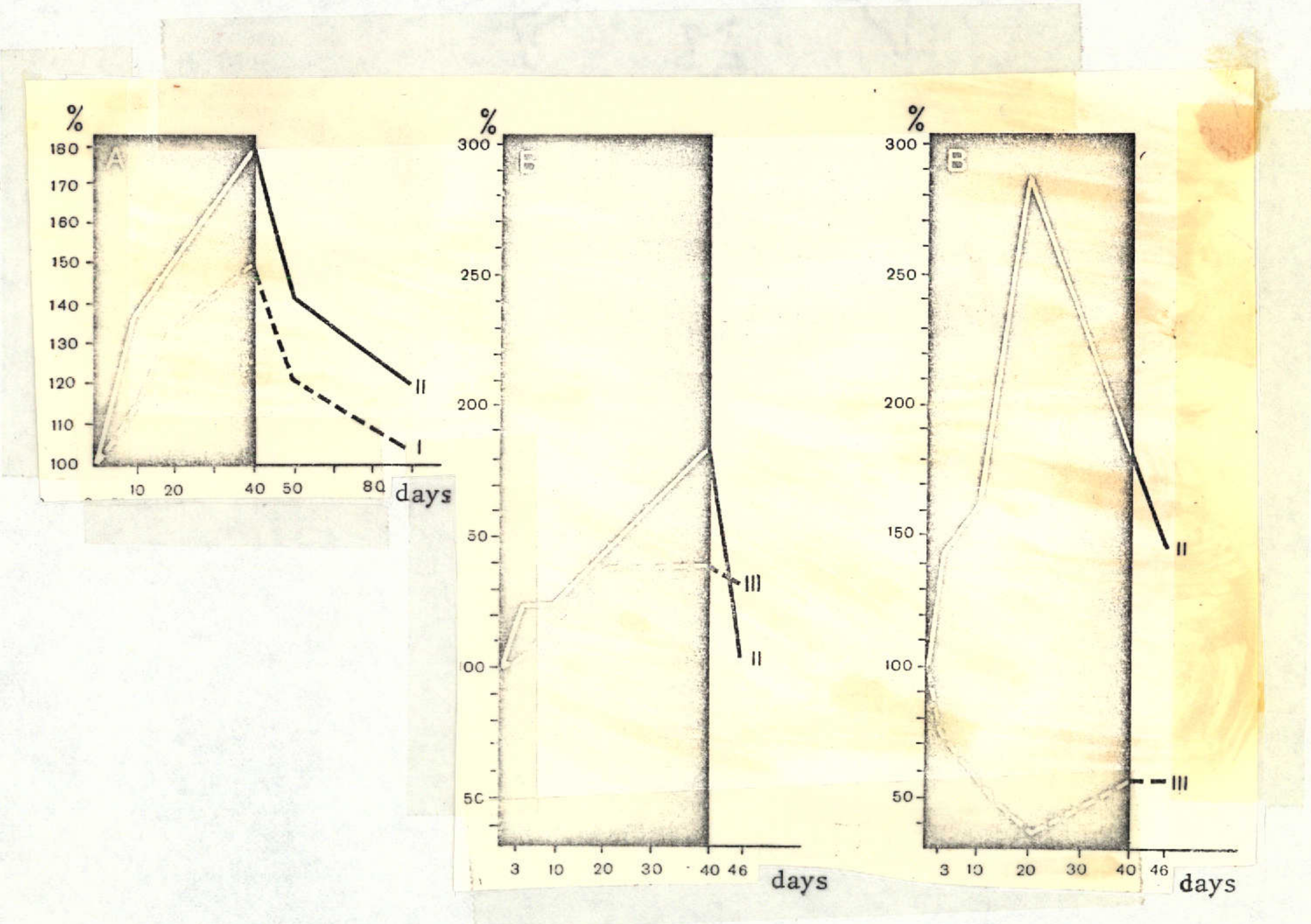


Fig. 3. Changes in the ceebral cortex in the process of adaptation to hypoxia:
A - Dynamics of RNA concentration (I) and protein synthesis (II) in the cortex;
B - Dynamics of the synthesis of protein (II) and the dimensions of giant pyramid neurons (III);
C - Dynamics of protein synthesis (II) and the dimensions of nuclei of glial cells (III), adjacent to the pyramid neurons. An increase in the concentration of RNA and adaptation of protein synthesis in the cortex in the process of adaptation to hypoxia develop gradually. The synthesis of protein is activated both in the pyramid neurons and in the glial cells, but the size of the neurons increases, while the size of the nuclear glial cells, on the other hand, decreases.

overwhelming majority cardiac muscle cell mitochondria. Consequently, during adaptation to altitude hypoxia one observes a selective activation of the formation and a significant increase in the quantity of mitochondrial DNA. This signifies an increase in the overall content of the mitochondrial genomes and as an intermediary - via the system of mitochondrial RNA - can play an important role in the activation of synthesis of mitochondrial proteins.

In the myocardium of the right ventricle, the intensity of mitochondrial RNA synthesis more than 2-fold (fig. 5). During the process, the dynamics of synthesis of mitochondrial RNA entirely coincides with the dynamics of concentration of mitochondrial DNA. This coincidence is very important. It enables one to imagine that the intensity of transcription in the mitochondria is determined by the amount of available genetic matrices. Consequently, during adaptation to hypoxia, the intensity of synthesis of mitochondrial RNA increases because there is an increase in the number of such matrices.

We shall now compare the dynamics of RNA synthesis in the nuclei and in the mitochondria of the myocardial cells of the right ventricle (fig. 6 A). One can see that 20 days following the beginning of adaptation, activation of RNA synthesis (transcription) in the nuclei mitochondria reaches a maximum; the intensity of synthesis in the nuclei increases 3-fold while undergoes a 2-fold increase in the mitochondria. This predominance of activation RNA synthesis in the nuclei, in comparison with the mitochondria, agrees with the well known concept that /78
only structural protein of the mitochondria is synthesized on the basis of information coded in the mitochondria DNA and RNA. All remaining protein, specifically the respiratory enzymes of the mitochondria are synthesized on the basis of information coded in the nuclear DNA and RNA, i.e., in the nuclear genome.

Hence, an increase in the synthesis of the entire complex of mitochondrial protein and the formation of the mitochondria can occur only as the result of a simultaneous and coordinated activation of the nuclear and mitochondrial genomes of the cell.

Bearing this in mind, one can examine the dynamics of the synthesis of mitochondrial proteins in the cardiac muscle (fig. 6). The intensity of synthesis of the mitochondrial proteins in the right ventricle increases at the tenth day of adaptation three-fold, and subsequently somewhat decreases. It is extremely signficant that the degree of observable activation of synthesis of the mitochondrial proteins is 2-3 timer than the degree of activation of synthesis of the sum protein of the myocardium in our experiments which were conducted earlier.

This fact reflects the predominance of mitochondrial proteins with general activation of synthesis under conditions of adaptation.

The adaptation significance of biogensis of the mitochondria during hypoxia, apparently, consists in the following. The oxygen deficiency which has appeared decreases the formation of ATP of each mitochondrium. Consequently, the formation of ATP per unit of tissue mass also decreases. In response to this, formation of the mitochondria is activated and the number of these organelles per unit of tissue mass increases. Such a change, so extensive in its essence, restores or even increase the formation of ATP per unit mass of cell, and increases the capacity of the cell to utilize oxygen from the blood and to restore the formation of ATP per unit mass of tissue. As a result of the described changes, the disruption of functions which appeared primarily as the result of a deficit in ATP is eliminated, notwithstanding the still existent deficiency of oxygen and the decreased formation of ATP of each mitochondrium.

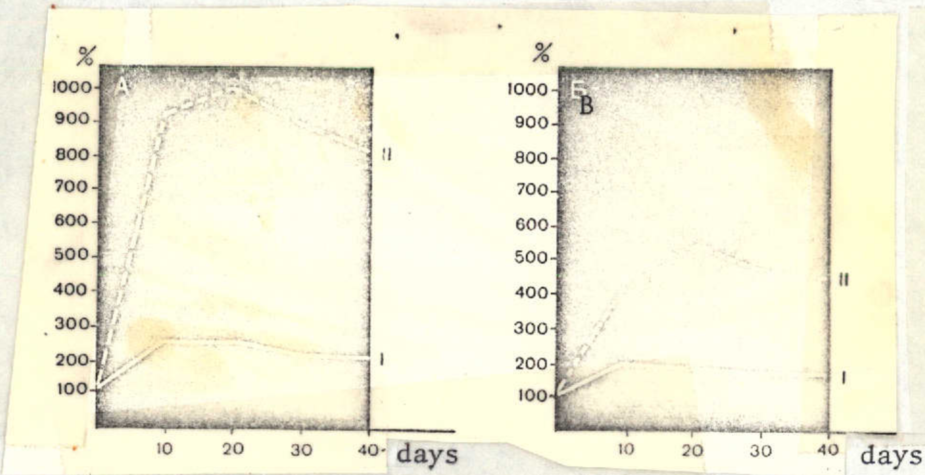


Fig 4. Dynamics of concentration (I) and synthesis (II) of mitochondrial DNA in the myocardium of the right (A) and left (B) ventricles in the process of adaptation (symbols along the axes of the coordinates are the same as in fig. 1).

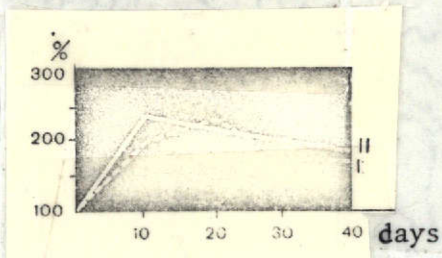


Fig. 5. Dynamics of RNA synthesis (I) and of the concentration (II) of DNA in the mitochondria of the right ventricle during adaptation (symbols along the axes of the coordinates are the same as in figure 1).

imp/min

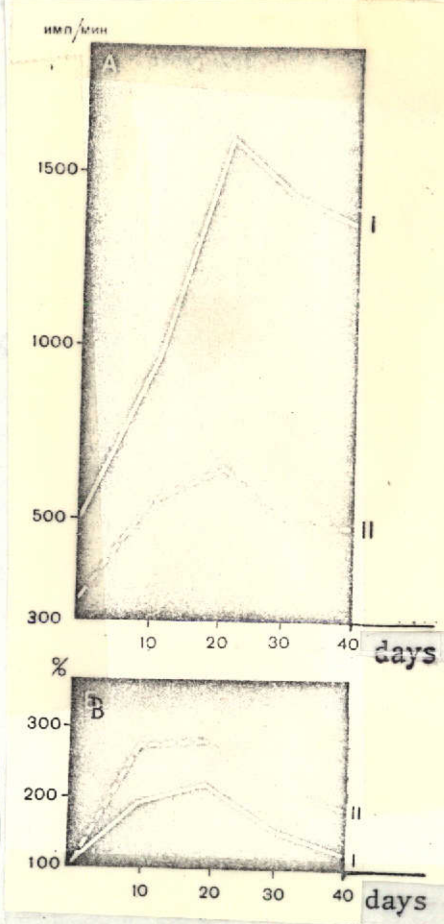


Fig. 6, Dynamics of RNA synthesis (A) and protein synthesis (B) in the nuclei (I) and mitochondria (II) of the myocardium during adaptation. Graph A along the axis of the ordinate - specific activity of RNA (intensity of inclusion of labeled orotic acid, n imp/min per 100 mg). In graph B along the axis of the ordinate, - an increase in the synthesis (in %). Both graphs indicate an increase in synthesis as the result of a simultaneous and coordinated activation of the nuclear and mitochondrial genomes of the cell.

The Common Aspect of the Mechanism of Adaptation to Environmental Factors

In order to understand the mechanism of activation of protein synthesis and of the increase in the formation of the mitochondria during hypoxia, it should be born in mind that this reaction appears not only in response to hypoxia, but also in response to the effect of any particular factor which cause a deficit in the macroergic phosphates in the cells. This is indicated by data of recent years. Thus, it has been demonstrated during intensive and long term stresses, the resynthesis of ATP in the heart, the muscles, and the neurons can signficantly /79 lag behind the expenditure of ATP on functions. As a result, a decrease in the concentration of ATP and creatin phosphate appears, which is principally accompanied by activation of synthesis of nucleic acids and proteins, and primarily by an increase in the formation of mitochondria.

Another factor - cold - causes, as is known, a lack of coordination in the processes of oxidation and phosphorylation in the mitochondria and thús leads to a significant decrease in the concentration of energy-rich phosphorous compounds (macroergs). It has been shown that during the process activation of nucleic acid and protein synthesis occurs, as well as an increase in the formation of mitochondria.

These facts have urged the author to the hypothesis which is, in a simplified form, shown in figure 7. The essence of this hypothesis consists in that three main factors of the environment - physical stress, hypoxia, and cold - to which the organism adapts, and acting in various ways, in the final analysis lead to the very same overall change - a deficit of the energy which phosphorous compounds and an increase in the phosphorylation potential. This primary change acts as a signal, which, as the result of the mechanism yet requiring further study, activates the genetic apparatus of the cells.

Recent investigations have shown that an important role in this mechanism is played by the cyclic adeninnucleotide three 'five AMP, which is a powerful inducer of the genetic apparatus.

Activation occurs along the line of a primary increase in the formation of mitochondria; as a result, the capacity of the system of the mitochondria increases and the processing of ATP per unit mass of tissue accomplished by the mitochondria increases.

Subsequently, as was shown in the diagram, activation of formation can develope - biogenesis of all cellular structures - and then the growth of cells leads to a decrease in the intensity of functioning of the structures (IFS). This change in its turn signals a decrease in the consumption of ATP per unit mass of the cell.

In total, the ATP deficit seems to be eliminated and a stable adaptation to hypoxia develops, as well as a stable adaptation to significant stresses into cold. Our hypothesis presumes that adaptation of the organism to primary factors of the environment is provided for by the utilization of the very same commom method - activation of biogenesis of mitochondria and by an increase in the capacity of the system of oxidation resynthesis of ATP per unit mass of cell. Such a reaction of the genetic apparatus of the cell forms, to our view, a necessary fundamental aspect of the organism's adaptation to the environment, caused by the influence of higher levels of regulation which, in its turn, significantly influences the condition of the brain and the endocrine system.

The place of this aspect in the complex mechanism of adaptation of the entire organism is determined to a lesser degree by three lines of regulatory interactions.

First, basic factors of the environment act in an intermediate fashion through neuroendocrine mechanisms, and as a result of this all changes presented in the diagram, beginning with the deficit of macroergs, and concluding with activation of mitochondrial biogenesis, turn out to be, to a significant extent, caused by "descending" regulatory effects, i.e., by the effect of concrete mediators and hormones, whose effect is addressed to the key aspects of the cellular mechanisms of self regulation.

Secondly, following the development of a chain of phenomena shown in the diagram, the increase in the capacity of the mitochondrial system which has occurred as a significant "descending" effect on the activity of the physiological systems of the organisms which play an important role in adaptation. Thus, as a result of the chain of changes shown in the diagram, the cells acquire the capacity to absorb an increased amount of oxygen from the unit of volume of the flowing blood. This phenomena was well studied by N.V. Lauer and A.Z. Kolchinskaya[1] and other investigators, leads to the conclusion that the necessary consumption of oxygen can be achieved at a lesser pulmonary ventilation and through a lesser minute volume of the heart. In full agreement with this, mobilization of the transport systems, sharply pronounced in the initial period of action of hypoxia, principally decreases proportional to the development of adaptation, as is known.

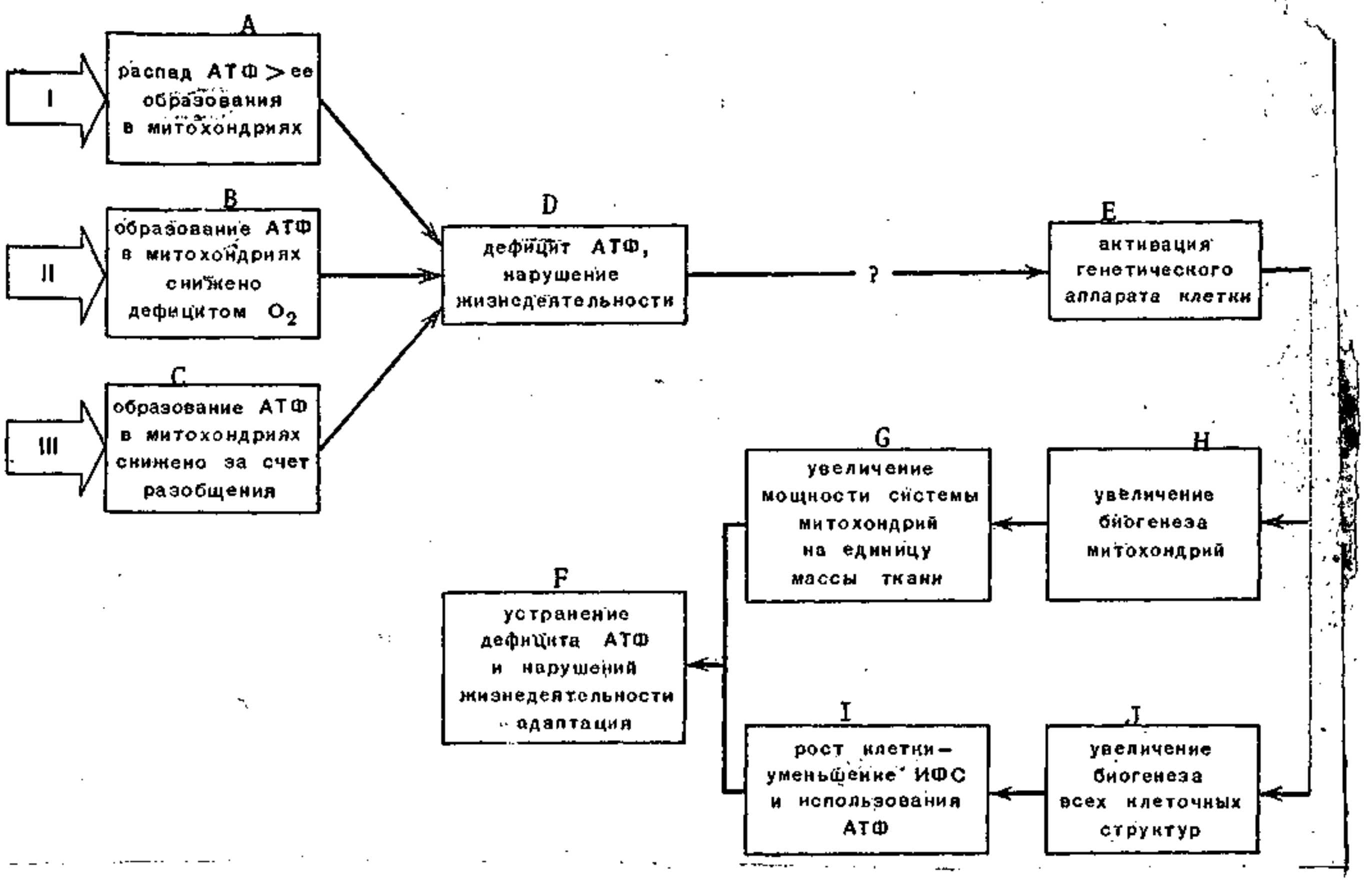
Hence, the development of adaptational changes at the level of the cells halts the descending influence, offering the architecture of the adaptational process, changing it into a maximally economical regime of the organism's resources.

The third line of interaction between the cellular level and the level of the organism as a whole in the process of adaptation consists in the fact that activation of synthesis of nucleic acids and proteins, which develops on a base as shown in the diagram above in the neurons and glia of the brain, has a deep effect on the functional capacities of the brain and thus on the behavioral reactions of the organisms under new environmental conditions. It has been shown in our laboratory that pronounced activation of synthesis of nucleic acids and proteins and an increase in the activity of the mitochondrial enzymes which develop in the cerebral cortex during adaptation altitude hypoxia is accompanied by a hastening in the development of conditioned reflexes, by a quickening in the process of consolidation of memory, and by an increase in the resistance of the brain to extreme stimuli. In other words, events unfolding during adaptation at the cellular level of the brain can significantly determine the behavioral reactions of the entire organism under complex environmental conditions.

Examining, thus, adaptation to altitude hypoxia as a complex reaction the entire organism it is also additional necessary in an entirely determined fashion to emphasize that an increase in the capacity of the oxygen transport systems and the system of ATP oxydation resynthesis is the most important component of this reaction. It should be born in mind that it is in fact the deficiency of the systems of energetic support which comprises the significant element of pathogenesis of many deseases of the circulation and brain.

1 In the collection: Kislorodnyy Rezhim Organizma I Yego Regulirovaniye The Oxygen Regime of the Organism and its Regulation. Kiev, 1966.

On this basis we investigated preliminary adaptation to altitude hypoxia for prophylaxis of experimental diseases of circulation and the brain.



A - Deterioration of ATP its formation in the mitochondria

B - Formation of ATP in the mitochondria decreased by the O_2 deficit

C - Formation of ATP in the mitochondria decreased as a result of disorganization

D - Deficit of ATP, disruption of vital activity

E - Activation of the genetic apparatus of the cell

F - Elimination of the ATP deficit and disruptions of the vital activity - adaptation

G - Increase in the capacity of the mitochondrial system per unit mass of tissue

H - Increase in biogenesis of the mitochondria

I - Growth of the cell - decrease of IFS and use of ATP

J - Increase in biogenesis of all cellular structures

Fig. 7. Diagram of adaptation to the long term effect of environmental factors - physical stresses (I), hypoxia (II), cold (III).

PROPHYLACTIC EFFECTS OF PRELIMINARY ADAPTATION TO HYPOXIA

EXPERIMENTAL PATHOLOGY	EFFECT
I. CIRCULATION	
Experimental cardiac damage	Prevention of disorders of the contractile function of the heart and phenomena of cardiac deficiency
Experimental infarct of the myocardium caused by noradrenaline analogues	Decrease in the zones of injury, to the cardiac muscle and in disorders of the contractile function the heart
Experimental myocardial infarct caused by overloading the coronary artery	Decrease in the zone of damage to the cardiac muscle and in the disorders of the contractile functions of the heart
Experimental hypertony	Decrease in the degree of hypertony or its prevention
II. BRAIN	
Convulsions caused by corazol	Decrease in the duration of onsets; increase in the latent period
Convulsions similar to epileptic seizures, caused by a loud noise	Prevention or treatment
Disorder of learning caused by a hallucinogen (lysergic acid diethylamide - LSD)	Total prevention

Prophylaxis of Damage to the Heart and Brain

The basic prophylactic effects of preliminary adaptation to altitude hypoxia studied in the laboratory are enumerated in the table. It is indicated that this type of adaptation can entirely prevent severe cardiac deficiency caused by experimental damage to the heart and can significantly decrease disorders of the structure and function during experimental myocardial infarcts, as well as inhibit the development of experimental hypertony in animals. This is also been shown that preliminary adaptation to hypoxia prevents the so-called sonic experimental epilepesy, and significantly decreases convulsions which appear following the administration of corozol, and also prevents disorders developed in animal conditioned reflexes by small doses of LSD. /81

It is expedient to examine certain of the prophylactic effects in somewhat greater detail. The most interesting results were obtained in experiments conducted by the author and O. A. Gomazkov[1], during a study of the influence of preliminary adaptation to hypoxia on the course of myocardial infarct caused by ligature of the left coronary artery in the rat. The following ligature of this artery, over the course of succeeding days, more than half of the unadapted animals died and only 9% of the animals preliminarily adapted to hypoxia died. This difference

1 "Kardiologiya", 1972, Nr. 10.

in lethality becomes clear during an estimation of the contractile function of the heart in adapted and unadapted animals with experimental infarct (fig. 8). The entire configuration of the curve of the contractile cycle in rats adapted to altitude hypoxia is different than that of among animals not adapted - the cycle is differentiated by a more rapid development of the contractile processes and the weakening processes, and also by a somewhat higher systolic pressure. These differences are clearly pronounced both under conditions of physiological calm, and during stress caused by short term pressure on the aorta. Following creation of the infarct, the defect in the contractile function, characterized in the drawing by the magnitude of the shaded zone, turns out to be incommensurately less among adapted animals then among unadapted animals. Hence, one can consider it proven that preliminary adaptation to altitude hypoxia during experimental myocardial infarct has a prophylactic effect.

During a study of the effect of preliminary adaptation on the resistance to strong sonic stimulation, which in the rat caused lines of Krushinskiy-Molodkina convulsions similar to epileptic convulsions, no less convincing results were obtained. In these experiments, which were conducted jointly with M.YA. Mayzelis, it became clear that proportional to the development of adaptation to hypoxia, convulsion in response to sound in 60% of the animals ceased to appear, while in the remaining rats they became less prolonged.

Evaluating these results, it is necessary to bear in mind that experimentally caused diseases of animals differ fundamentally from human disease. Therefore it does not follow mechanically to transfer into the clinic the results of successful prophylaxis as obtained in the experiment. Additionally, these results serve as a justifiable point of departure for special clinical-physiological investigations should answer the question whether or not adaptation to discontinuous hypoxia can be used for preventing circulatory diseases and brain diseases in man.

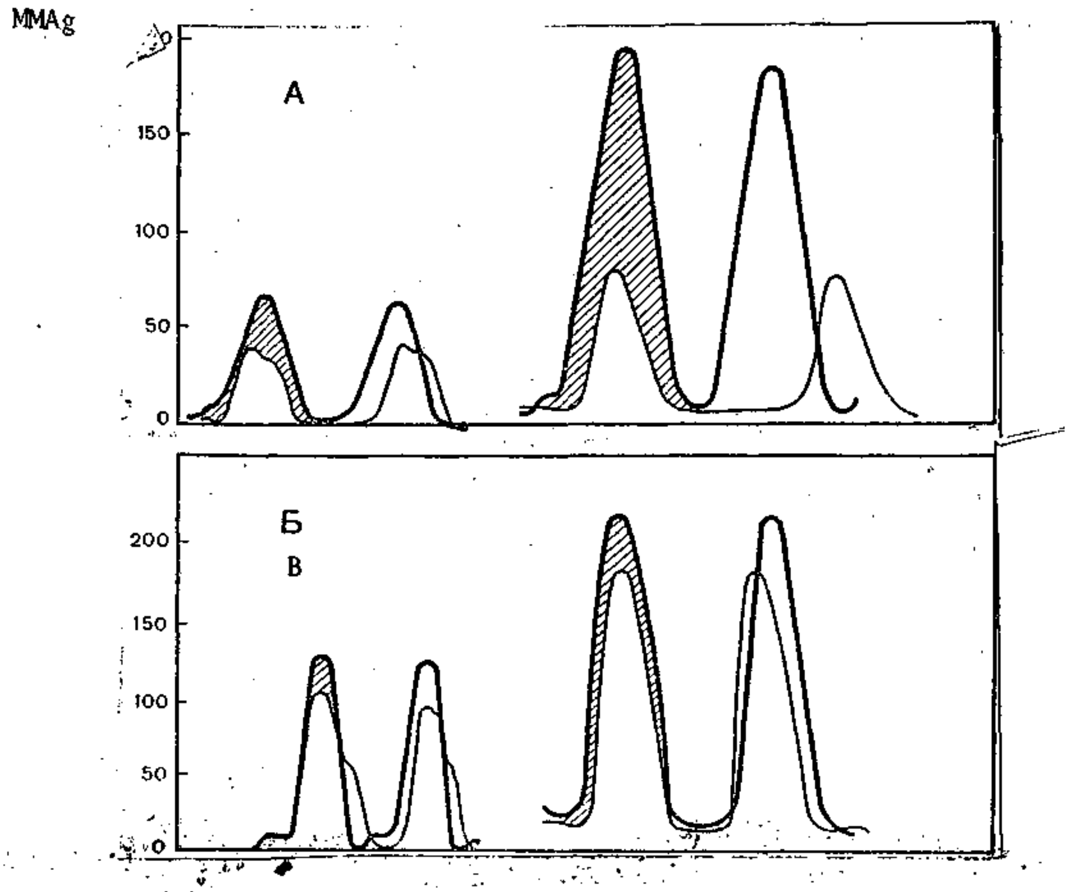


Fig. 8. The prophylactic effect of adaptation to hypoxia during experimental infarct in the rat. Change in pressure in the left ventricle in unadapted (A) and adapted (B) animals one day following ligature of the left coronary artery: heavy lines - curves of pressure for rats without infarct, fine lines - for rats with experimental infarct; from the left - recordings of pressure during relative physiological calm, from the right during stress (short term pressure on the aorta). The shady zone shows the magnitude of defect in the contractile function of the heart following infarct.

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